

## Chapter 1

# PHYSICAL MECHANISMS OF SOFT TISSUES RHEOLOGICAL PROPERTIES

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Soft tissues rheology is determined by their internal structure and by their constituents' properties and mutual interactions. Specifics of these relationships are analyzed in terms of four constitutive properties: 1) The tissues' non-linear stress-strain relationship is consistent with their collagen fibers non-uniform undulation and gradual straightening with stretch. Response anisotropy is attributed to the fibers non-uniform orientation distribution. 2) The fibers gradual recruitment is also consistent with the tissues' viscoelastic non-linearity. It is shown that under protocols where no fibers buckle (e.g., stress relaxation and creep tests) the fibers recruitment process is compatible with the quasi-linear viscoelastic theory. 3) Preconditioning adaptation of tissues to its loading is an essential response feature, induced by the preconditioning properties of the fibers. The latter are both strain and time dependent. Excellent fit to data of multiple uniaxial (tendon) and biaxial (skin) data is obtained only if preconditioning is incorporated into the constitutive formulation. 4) Residual stress in unloaded state stems from three levels of interactions between the tissues' constituents (the micro, meso and macro levels, respectively), which must all be relieved if a true stress-free reference is desired. In summary, modeling based on structural consideration provides mechanistic insights and facilitates reliable constitutive formulation.

### 1. Introduction

Y.C. Fung established the foundations for studies of soft tissues mechanics based on the concepts of quasi-linear viscoelasticity, preconditioning and residual stress. In parallel, attempts have been made by Fung and others to model these response features and establish their validity. Here we analyze the mechanistic origins of these rheological characteristic based on the tissue structure, the constituents' properties and their mutual interactions, and show how these considerations facilitate reliable representation of the tissue constitutive properties.

## 2. Analysis and Results

### 2.1. *Tissues Nonlinear Stress-Strain Relationship*

The tissues uni-axial stress-strain response is convexly non-linear – the tissue becomes stiffer with increasing strain. Fung [1] proposed an exponential type uniaxial stress-strain relationship which was later generalized to multi-dimensions [2] and applied by Fung and others to the aorta [3], arteries [4], the lung tissue [5], the skin [6] and to other tissues.

*Fibers recruitment in the tendon:* A first clue to the possible origin of tissues' non-linearity was provided by Viidik [7, 8]. He observed in tendon that while at rest all collagen fibers are undulated, upon stretch there is a process of gradual fibers recruitment during the non-linear “toe” region. This is followed by a linear response when all fibers are straight. A similar process was observed under biaxial stretch of the mesentery [9]. Hence the stress-strain non-linearity may stem from gradual recruitment of fibers: with increasing stretch, more fibers become active (stretched), thus increasing the tissue stiffness. Based on these experimental observations, a mathematical framework was developed for incorporating the intrinsic properties of the fibers and their waviness distribution into constitutive laws [10-13].

For “elastic” fibers, the strain-energy function  $w_f$  of an individual fiber is a function of its uniaxial strain  $e_f$ . Based on Viidik and others it is assumed that the long and thin fibers possess only axial tensile stiffness and their compressive and bending stiffness are negligible. Hence the fiber transmits only axial force and only when stretched. Its second Piola-Kirchoff axial stress is given by  $s_f = \partial w_f(e_f) / \partial e_f$ , with  $s_f(e_f \leq 0) = 0$ . Since the uniaxial response of the tendon is linear when all fibers are stretched, then this suggests that the intrinsic fiber stress-strain law  $s_f(e_f)$  is also linear, or very close to it. If the fiber is wavy at rest, then the true fiber's strain is related to the global finite Lagrangian strain  $e$  by [13]:

$$e_f(e, e_s) = (e - e_s) / (1 + 2 \cdot e_s) \quad (1)$$

where  $e_s$  is the fiber straightening strain. The uniaxial strain-energy function of the entire population of parallel and non-uniformly undulated collagen fiber-bundle  $W_b$  is equal to the sum  $w_f$  of all fibers:

$$W_b(e) = \int_0^e \hat{D}(x) \cdot w_f[e_f(e, x)] \cdot dx, \quad w_f(e_f \leq 0) = 0 \quad (2)$$

where  $\hat{D}(x)$  is the waviness density distribution such that the fraction of fibers becoming straight between the strain levels  $x$  and  $x+dx$  equals  $\hat{D}(x) \cdot dx$ . Physically, the straightening strain  $x$  represents the fiber's stress-free gage-length. From the theory of hyper-elasticity, the second Piola-Kirchoff uniaxial stress of the entire fiber bundle is given by:

$$S_b^e(e) = \partial W_b(e) / \partial e = \int_0^e \hat{D}(x) \cdot \frac{\partial w_f(e_f)}{\partial e_f} \cdot \frac{\partial e_f}{\partial e} \cdot dx \quad w_f(e_f \leq 0) = 0. \quad (3)$$

Using Eq. 1 and substituting the stress  $s_f$  for  $\partial w_f(e_f) / \partial e_f$  in Eq. 3 one gets:

$$S_b^e(e) = \int_0^e D(x) \cdot s_f(e_f) \cdot dx \quad s_f(e_f \leq 0) = 0 \quad (4)$$

where  $D(x) = \hat{D}(x) / (1 + 2x)$  is the modified waviness distribution function. Eq. 4 is the uniaxial elastic stress-strain law for the gradually recruiting fiber bundle. Importantly, although the stress-strain law  $s_f(e_f)$  of the individual collagen fiber is linear, the response of the fiber bundle is convexly non-linear due to the gradual recruitment of fibers.

*Generalization to 3D tissues:* Unlike the tendon, most tissues consist of multi-dimensional networks of different types of fibers (e.g., collagen, elastin). Extension of the above structural approach to the general three dimensional case is straightforward by incorporating into the model the fiber orientation distribution [11, 13]. Tissue anisotropy is induced by non-uniform orientation distribution of its fibers.

Models based on these concepts have been developed for the tendon [14], the aortic valves [15, 16], the pericardium [17], the skin [11, 18, 19] the myocardium [20, 21] and blood vessels [22, 23].

*Other structural models:* A different class of structure-based models considers the collagen fiber as a rod whose non-linear uniaxial stress-strain response stems from its bending (or bending and twisting) during its gradual flattening with stretch, usually following Euler's elastica theory. The shapes considered were planar zigzag [24, 25], planar wavy [26] and helical [27, 28]. In reality however, a rod cannot reliably represent the collagen fiber since the latter is a multi hierarchy aggregate containing axial subunits (collagen molecule, micro-fibril, sub-fibril, and fibrils) interconnected laterally by various cross-links being all distinctly different in nature from the collagen molecules. In addition, unlike the rod, subunits as well as the whole fiber respond differently to tension versus compression and probably buckle under negligible small compressive load.

## 2.2. *Tissues Quasi-Linear Viscoelasticity*

Soft tissues manifest viscoelastic characteristics [2]. Fung observed that under many circumstances, the tissue response can be separated between an immediate (“elastic”, i.e., time-independent) non-linear stress-strain relationship, and a strain-independent function of time. The resulting quasi-linear viscoelastic (QLV) theory [1] carries a significant advantage over non-linear viscoelastic theories by being compatible with the mathematical machinery of linear viscoelasticity. QLV is currently the most widely used viscoelastic representation for soft tissues. Fung [1] formulated the QLV law in two alternative forms,

$$S(e, t) = \int_0^t G(t-\tau) \cdot \dot{S}^e[e(\tau)] \cdot d\tau, \quad S(e, t) = \int_0^t G(t-\tau) \cdot \frac{dS^e}{de} \cdot \dot{e}(\tau) \cdot d\tau \quad (5)$$

where  $G(t)$  is the reduced (normalized) relaxation function and the dot designates time derivative. Eq. 5a relates the current stress  $S(e, t)$  to the history of the instantaneous (“elastic”) response  $S^e[e(t)]$ , while the alternative (and equivalent) form (Eq. 5b) relates the current stress to the strain history  $e(t)$ .

*Viscoelasticity and fibers recruitment:* Assuming that the fibers are linear viscoelastic, then the viscoelastic stress in the fiber is given by the Boltzman hereditary integral (in analogy to Eq. 5a), as follows:

$$s_f(e_f, t) = \int_0^t G(t-\tau) \cdot \dot{s}_f^e[e_f(\tau)] \cdot d\tau \quad (6)$$

where  $s_f^e(e_f)$  is the immediate (“elastic”) response of the fiber. The viscoelastic stress in the fiber bundle is obtained by summing the contributions of all fibers as in Eq. 4:

$$S(e, t) = \int_0^e D(x) \cdot s_f[e_f(x, t), t] \cdot H(s_f) \cdot dx \quad (7)$$

where  $H$  is the unit step function which guaranties that the stress in buckled fibers will be taken as zero. Eqs. 6 and 7 prescribe the viscoelastic response of the tendon fiber bundle.

It was recently shown [29], theoretically, numerically and experimentally, that in fully preconditioned tendon (see below), under protocols at which no

fiber buckles, the system of equations 6, 7 is equivalent to the QLV theory. If no fiber buckles then two consequences result: first, the fiber viscoelastic stress  $s_f(e_f, t)$  in fibers that were stretched during the protocol is always positive, so that  $H \equiv 1$ . Eq. 6 can then be substituted into Eq. 7 to yield:

$$S(e, t) = \int_0^e D(x) \cdot \int_0^t G(t-\tau) \cdot \dot{s}_f^e[e_f(\tau)] \cdot d\tau \cdot dx \quad (8)$$

In addition, since no fiber buckles then the argument functions are single-valued so that the order of integration in Eq. 8 can be interchanged, resulting in:

$$S(e, t) = \int_0^t G(t-\tau) \cdot \int_0^e D(x) \cdot \dot{s}_f^e[e_f(\tau)] \cdot dx \cdot d\tau = \int_0^t G(t-\tau) \cdot \dot{S}^e[e_f(\tau)] \cdot d\tau \quad (9)$$

The second equality (derived by using Eq. 4) is identical to the expression for the QLV stress (Eq. 5a). If on the other hand fibers do buckle, then their stress vanishes for all  $S_f \leq 0$  and their stress-strain relationship is flat and thus no longer single-valued.

Hence, the tissue nonlinear viscoelastic features stem from its fibers gradual recruitment. Furthermore, micro-structural considerations show that the tendon viscoelastic response is reliably represented by the QLV theory if no fibers buckle during the stretch protocol. Importantly, this condition is met during both stress relaxation and creep tests.

### 2.3. Tissues Preconditioning

In addition to viscoelasticity, experimental observations commonly manifest another time-dependent response feature: under repeated cycles of stretch, there is a decay and shift to the right of the stress-strain response. This preconditioning adaptation process is at times only partially reversible, and requires rest periods which are orders of magnitude longer than characteristic viscoelastic relaxation times. The concept of preconditioning was introduced to tissue biomechanics by Fung [30] who proposed that constitutive formulation should be based on stable response obtained from fully adapted (preconditioned) tissue samples. Previous attempts to model tissue preconditioning were phenomenological (not relating to the tissue structure). Preconditioning was represented by the strain softening (Mullins) effect in arrested left ventricle [31] and in the small intestine [32]. Rubin and Bodner [33] incorporated

preconditioning in a phenomenological elasto-viscoplastic model for the skin, consisting of a composite of elastic and dissipative components. Sverdlík and Lanir [14] proposed that tissue preconditioning under stretch results from, and can thus be reliably modeled, based on the preconditioning response of its fibers.

*Preconditioning of tissues' fibers:* Experimental observations revealed that the physical processes of preconditioning in collagen and elastin fibers are mutually different. In collagen [34, 35], the fibers' stress-free length (gage-length) was observed to increase during preconditioning as a function of stretch and time, but the slope of the fibers' stress-strain relationship seems to be preserved [14]. In the recruitment model (Eq. 3), this process implies a gradual increase of the straightening strain  $x$ , which increases during preconditioning as a function of stretch and time. It was found [14] that two processes are required to adequately account for the tendon's collagen preconditioning: a rate ("viscous") process and a plastic one. Good agreement with data under multiple stretch protocols to different strain levels was obtained assuming a linear dependence of the viscous process on the fiber strain as follows:

$$\frac{dx}{dt} = \begin{cases} p_{1c}(e_f - p_{2c}), & e_f > p_{2c} \\ 0, & e_f \leq p_{2c} \end{cases} \quad (e_f = (e - x)/(1 + 2x)) \quad (10)$$

with initial condition  $x|_{t=0} = x_0$ , where  $x_0$  is the distributed reference waviness. Here  $p_{1c}(\geq 0)$  is a positive rate constant, and  $p_{2c}(\geq 0)$  is the threshold below which there is no viscous preconditioning. The second process is a perfect plastic one above a strain threshold [14], so that:

$$\frac{dx}{dt} = \frac{de_f(t)}{dt} \quad e_f > p_{3c} > 0; \quad \frac{de_f(t)}{dt} > 0 \quad (11)$$

$$\frac{dx}{dt} = 0 \quad \text{otherwise}$$

where  $p_{3c}(\geq 0)$  is the threshold.

In elastin fibers the extent of preconditioning-induced stress decay is smaller than in collagen, and the gage-length seems to be preserved [19]. There is however a decay of the fibers stiffness. This type of preconditioning adaptation is termed "strain softening" or Mullins effect [36]. Mullins attributed the magnitude of stiffness reduction in rubbers and polymers solely to the highest level of previously imposed strain. In contrast, our observations revealed that elastin strain softening is also time-dependent. Good fit to uniaxial stretch

data of the skin [37] at the elastin dominated low strain levels was obtained [19] when the elastin stiffness was assumed to decay with time from its reference level in a first order process depending linearly on the strain.

The structure-based mechanistic approach to modeling preconditioning in tissues was applied for the tendon [14], and for the skin under both uniaxial [19] and biaxial [38] deformations. It was shown that preconditioning is an essential response feature and that a reliable representation of responses under multiple uniaxial and biaxial (Fig. 1) tests is obtained only if preconditioning is incorporated into the constitutive equations.

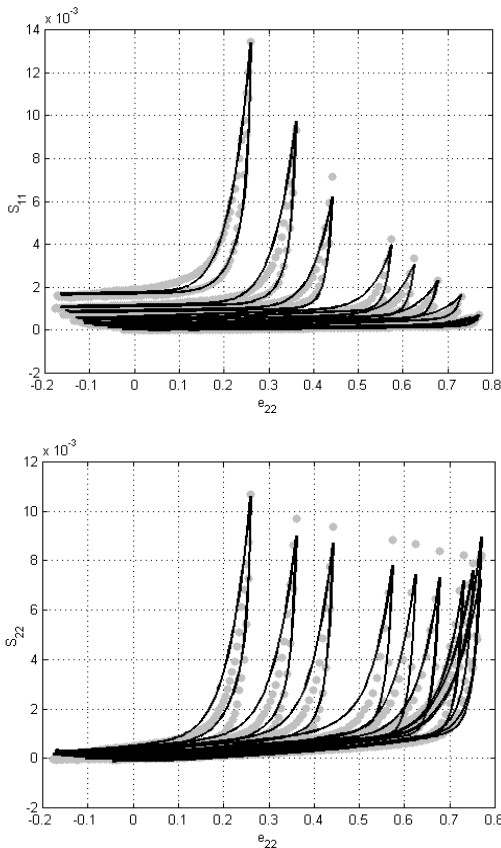


Figure 1. Comparison between Measured Skin Biaxial Response (circles) and Model Predictions (dark line) for Stress Components  $S_{11}$  (upper panel) and  $S_{22}$  (lower panel) to Multiple Level Constant Rate Stretch in the 2-Direction.

## 2.4. *Tissues Residual Stress*

Chuong and Fung [39] found that arteries, rather than being stress-free in the unloaded state (i.e., free vessel segment, zero pressure) are internally loaded by residual stress (RS). When a vessel ring is cut longitudinally, it springs open to a presumably truly stress-free configuration with an opening angle (OA) whose magnitude is a measure of the RS. Similarly, OA was later found also in myocardial left ventricle rings [40]. Importantly, Fung and coworkers [39-42] later showed that RS significantly affects the tissue's stress and strain distributions, and that it carries substantial functional benefit by reducing stress concentration near the internal surface in these organs, thereby reducing their energy consumption.

The importance of knowing the level of RS and the related stress-free configuration is two-fold. First, the stress-free configuration of the organ is an essential reference needed to evaluate the true stress and strain which is exerted on the tissue's cells, thereby determining their biological signaling response and the ensuing tissue biological remodeling. Second, often RS are associated with increased stiffness of the tissue. This stiffening, is likely to modify the tissue function.

*Mechanisms of RS:* The mechanistic origin of tissues' residual stress is yet unclear. In a recent report [43] it was proposed that there is a hierarchy of different RS producing mechanisms. The micro level (tissue interstitium) RS is induced by local interactions between the tissue constituents (fibers, cells, ground substance matrix). The second meso-level RS results from internal interactions induced by non-homogeneities in the tissue micro-structure or constituents composition. This meso RS is determined by several factors including the local micro RS, the mechanical interactions between composite tissue elements (e.g., between the media and adventitia in the arterial wall [44]), and by in-homogeneity in the tissue mechanical properties [45]. The third, macro (organ) RS arises from kinematical constraints on the tissues structures which produce additional internal loading (e.g., forces and bending moments required to close the wall into an intact vessel).

The implication of this hierarchy of RS producing mechanisms is that a true stress-free state can only be achieved if all RS mechanisms are neutralized. Relieving just one source of RS such as a radial cut through the arterial wall is insufficient and may leads to erroneous estimate of the state of stress and strain in the tissue.

*The micro-level RS:* While the macro- and meso-levels RS are fairly well studied and defined [39, 41, 42, 45-52], the mechanism underlying the micro-

level one are still unclear. Yet its existence has been experimentally verified in both the left ventricle [53] and in arteries [44, 54]. A recent analysis based on the tissues' multi-constituents structure and on the mixture theory [43], suggests that micro-level RS can stem either a) from contact stresses between the tissue's solid constituents resulting from their incompatible growth and remodeling [55, 56], or b) from the mechanical interaction between the solid constituents and the extra-cellular swelling-induced fluid pressure. This interaction can be understood from the following mixture theory equation relating the total stress  $T^{tot}$  to the stress  $T_i^s$  of the solid constituent  $i$  and to the pressure of the extra-cellular ground substance  $P$ , and from the thermodynamic equilibrium equation between  $P$  and the osmotic pressure  $\pi^{osm}$ :

$$T^{tot} = \sum_i \phi_i \cdot T_i^s - P \quad P = \pi^{osm} \quad (12)$$

where  $\phi_i$  is the volume fraction of the  $i$ -th solid constituent. Eq. 12 shows that in the un-loaded state ( $T^{tot} = 0$ ), internal residual stress can exist as a result of mutual interaction between the solid constituents, or between them and the fluid osmotic pressure. The latter results from the osmotic Donnan effect of the negatively charged glycosaminoglycan (GAG) side chains in the large proteoglycans macromolecules (PG, primarily decorin and versican), which are immersed in the fluid-like matrix (the ground substance).

Analysis of previous experimental observations suggested [43] that under swelling levels similar to the *in vivo* ones, osmotic-induced tissue swelling is a major contributor to the micro-level RS. This conclusion is strongly supported by a recent study [44] on the aorta, in which it was possible to separate between the effects of swelling of smooth muscle cells on one hand, versus that of the extra-cellular space (which contains charged PGs) on the other. The results suggest that the osmotic charge effect in the extra-cellular matrix was the predominant underlying mechanism of the observed RS.

### 3. Discussion and Conclusions

The analysis presented here shows that tissues rheological response features can well be accounted for by their constituents' structure and properties, and their mutual interaction. Specifically, non-linearity and anisotropy result respectively from the fibers distributed undulation and from their non-uniform orientation distribution. The fibers gradual recruitment with stretch is also responsible for the tendon non-linear viscoelasticity, and the analysis shows that this micro-structural consideration is consistent with the QLV theory, but only if no fibers

buckle during the test protocol. Tissue preconditioning adaptation to the loading cycle is attributed to the preconditioning response of its fibers. Experimental observations suggest that the physical processes of preconditioning in collagen and elastin fibers are mutually different, but both are strain and time dependent. Finally, residual stress in unloaded tissues is attributed to interactions between constituents at three levels of organization, from the micro tissue space, via the meso tissue elements to the macro organ level.

The analysis presented here provides a unifying micro-mechanistic basis to various rheological response features of tissues. The merit of such a unifying outlook is that it can be readily generalized to other more complex structured tissues since all soft tissues are composed of similar constituents. In addition, results obtained thus far indicate that the structure-based approach provides for a reliable representation of the tissues properties.

## References

1. Y.C. Fung, *Biomechanics - Its Foundations and Objectives*, ed Y.C. Fung, N. Perrone, M. and M. Anliker, (Prentice-Hall, Englewood Cliffs, NJ, 1972), p. 181.
2. Y.C. Fung, *Biorheology*, **10**, 139 (1973).
3. T.T. Tanaka and Y.C. Fung YC, *J. Biomech.* **7**, 357 (1974).
4. Y.C. Fung, K. Fronek, P. and Patitucci, *Am. J. Physiol.* **237**, H620 (1979).
5. Y.C. Fung, *Circ. Res.* **37**, 481 (1975).
6. P. Tong and Y.C. Fung, *J. Biomech.* **9**, 649 (1976).
7. A. Viidik, *Z. Anat. Entwicklungsgesch* **136**, 204 (1972).
8. A. Viidik, *Int. Rev. Connect. Tissue Res.* **6**, 127 (1973).
9. B.M. Chu, W.G. Frasher, and H . Wayland, *Ann Biomed Eng* **1**, 182 (1972).
10. Y. Lanir, *J. Bioeng.* **2**, 119 (1978).
11. Y. Lanir, *J. Biomech.* **12**, 423 (1979).
12. Y. Lanir, *J. Biomech. Eng.* **102**, 332 (1980).
13. Y. Lanir, *J. Biomech.* **16**, 1 (1983).
14. A. Sverdlík and Y. Lanir, *J. Biomech. Eng.* **124**, 78 (2002).
15. K.L. Billiar and M.S. Sacks, *J. Biomech. Eng.* **122**, 327 (2000).
16. M.S. Sacks, *J. Biomech. Eng.* **125**, 280 (2003).
17. P.A. Shoemaker, D. Schneider, M.C. Lee, and Y.C. Fung, *J. Biomech.* **19**, 695 (1986).
18. S.M. Belkoff and R.C. Haut, *J. Biomech.* **24**, 711, (1991).
19. O. Lokshin and Y. Lanir, *J. Biomech. Eng.* **131**, 031009 (2009).
20. A. Horowitz, Y. Lanir, F.C Yin, M. Perl, I. Sheinman and R.K. Strumpf, *J. Biomech. Eng.* **110**, 200 (1988).
21. E. Nevo and Y. Lanir, *J. Biomech. Eng.* **111**, 342 (1989).

22. T.C. Gasser, R.W. Ogden, and G.A. Holzapfel, *J. R. Soc. Interface* **3**, 15 (2006).
23. M.A. Zulliger, P. Fridez, K. Hayashi, and N. Stergiopoulos, *J. Biomech.* **37**, 989 (2004).
24. C.P. Buckley, D.W. Lloyd, and M. Konopasek, *Proc. Roy. Soc. Lond.* **A372**, 33 (1980).
25. J. Diamant, A. Keller, E. Baer, M. Litt, and R.G. Arridge, *Proc. R. Soc. Lond. B. Biol. Sci.* **180**, 293 (1972).
26. M. Comninou and I.V. Yannas, *J. Biomech.* **9**, 427 (1976).
27. D.E. Beskos and J.T. Jenkins, *J. Applied Mechanics* **42**, 755 (1975).
28. D.C. Stouffer, D.L. Butler, and D. Hosny, *J. Biomech. Eng.* **107**, 158 (1985).
29. E. Raz, and Y. Lanir, *J Biomechanical Eng.* (Accepted 2009).
30. Y.C. Fung, *Biomechanics - Mechanical Properties of Living Tissues* (Springer- Verlag, New York, 1981).
31. J.L. Emery, J.H. Omens, and A.D. McCulloch, *J. Biomech. Eng.* **119**, 6 (1997).
32. H. Gregersen, J.L. Emery, and A.D. McCulloch, *Ann. Biomed. Eng.* **26**, 850 (1998).
33. M.B. Rubin, S.R. Bodner, and N.S. Binur, *J. Biomech. Eng.* **120**, 686 (1998).
34. Y. Lanir, E.L. Salant, and A. Foux, *Biorheology* **25**, 591 (1988).
35. M. Abrahams, *Med. Biol. Eng.* **5**, 433 (1967).
36. L. Mullins, *Rubber Chem. Technol.* **42**, 339 (1969).
37. H. Eshel and Y. Lanir, *Ann. Biomed. Eng.* **29**, 164 (2001).
38. O. Lokshin and Y. Lanir, *Biomaterials* **30**, 3118 (2009).
39. C.J. Chuong and Y.C. Fung, *J. Biomech. Eng.* **108**, 189 (1986).
40. J.H. Omens and Y.C. Fung, *Circ. Res.* **66**, 37 (1990).
41. Y.C. Fung, *Ann. Biomed. Eng.* **19**, 237 (1991).
42. Y.C. Fung and S.Q. Liu, *Am. J. Physiol. Heart Circ. Physiol.* **262**, H544 (1992).
43. Y. Lanir, *J. Biomechanical Eng.* **131**, 044506 (2009).
44. E. U. Azeloglu, M.B. Albro, V.A. Thimmappa, G.A. Ateshian and K.D. Costa, *Am. J. Physiol. Heart Circ. Physiol.* **294**, H1197 (2008).
45. L.A. Taber and J.D. Humphrey, *J. Biomech. Eng.* **123**, 528 (2001).
46. R.N. Vaishnav and J. Vossoughi, *J. Biomech.* **20**, 235 (1987).
47. T. Matsumoto, K. Hayashi, and K. Ide, *J. Biomech.* **28**, 1207 (1995).
48. X. Lu, A. Pandit, and G.S. Kassab, *Am. J. Physiol. Heart Circ. Physiol.* **287**, H1663 (2004).
49. S.Q. Liu and Y.C. Fung, *Diabetes* **41**, 136 (1992)
50. G.A. Holzapfel, G. Sommer, M. Auer, P. Regitnig, and R.W. Ogden, *Ann. Biomed. Eng.* **35**, 530 (2007).
51. H.C. Han and Y.C. Fung, *J. Biomech.* **24**, 307 (1991).

52. S.E. Greenwald, J.E. Moore Jr., A. Rachev, T.P. Kane, and J.J. Meister, *Biomech. Eng.* **119**, 438 (1997).
53. Y. Lanir, G. Hayam, M. Abovsky, A.Y. Zlotnick, G. Uretzky, E. Nevo, and S.A. Ben-Haim, *Am. J. Physiol.* **270**, H1736 (1996).
54. X. Guo, Y. Lanir, and G.S. Kassab, *Am. J. Physiol. Heart Circ. Physiol.* **293**, H2328 (2007).
55. E.K. Rodriguez, A. Hoger, and A.D. McCulloch, *J. Biomech.* **27**, 455 (1994).
56. R. Skalak, S. Zargaryan, R.K. Jain, P.A. Netti, and A. Hoger, *J. Math Biol.* **34**, 889 (1996).